DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Shefali Patel
Senior Manager, Regulatory Affairs
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Re: NDA # 22-081
Letairis™ (ambrisentan) tablets for oral use
MACMIS ID #17248

Dear Dr. Patel:

As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has become aware of oral statements made by a Gilead Sciences, Inc. (Gilead) representative on June 20, 2008, regarding its drug Letairis™(ambrisentan) tablets for oral use (Letairis). The representative's statements are false or misleading and minimize the serious risks associated with Letairis. Thus, this promotional activity misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(f)(1) and (n).

Background

According to its FDA-approved PI:

> LETAIRIS is indicated for the treatment of pulmonary arterial hypertension [PAH] (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening.

Letairis was approved under the Subpart H regulations, 21 CFR 314.520, with a risk management program, which includes a special restricted distribution program, the Letairis Education and Access Program (LEAP). The PI for Letairis includes a Boxed Warning regarding the risk of liver injury and the contraindication for use in pregnancy because of the risk of fetal harm. In addition, Letairis was deemed to have a risk evaluation and mitigation strategy (REMS) based on the elements to assure safe use in its risk management program.[1] The PI also contains Warnings and Precautions regarding hematologic changes, fluid retention, co-administration with cyclosporine A, and co-administration with strong CYP3A and 2C19 inhibitors. Adverse events that occurred in >3% of the patients receiving Letairis that were more frequent than in the placebo group were peripheral edema (17% vs. 11%), nasal congestion (6% vs. 2%), sinusitis (3% vs. 0%), flushing (4% vs. 1%), palpitations (5% vs. 2%), nasopharyngitis (3% vs. 1%), abdominal pain (3% vs. 1%), constipation (4% vs. 2%), dyspnea (4% vs. 3%), and headache (15% vs. 14%).

[1] See 73 Fed. Reg. 16,313, 16,314 (March 27, 2008).

False or Misleading Statements and Minimization of Important Risk Information

On Friday, June 20, 2008, at approximately 12:00 p.m., during the 2008 Pulmonary Hypertension Association International Pulmonary Hypertension Conference and Scientific Sessions in Houston, Texas, a Gilead representative stated:

> The [Letairis] risk management plan is only there because of the class. FDA only issued this because of the class, but this is not that big of a deal. Letairis has a 0.8% incidence of liver enzyme elevations versus 11% at the lowest dose of Tracleer. You cannot directly compare, but you can draw your own inference if you compare both PIs. . . .

These statements minimize the serious risks associated with the use of Letairis by misleadingly suggesting that the risks associated with the drug's risk management plan (potential liver injury and the risk of birth defects) do not apply to Letairis. Contrary to the representative's statements, the risk management program for Letairis was developed because of the risks associated with Letairis itself, which are also risks that are shared by other drugs in its class. The Boxed Warning section includes a discussion of liver enzyme changes observed in **Letairis** clinical trials representing "**a marker for potentially serious liver injury**" (emphasis in original). Due to this risk, the Boxed Warning emphasizes the importance of monitoring patients on Letairis, stating that "**serum aminotransferase levels … must be measured prior to initiation of treatment and then monthly**" and reinforcing "**the importance of strict adherence to the monthly monitoring schedule for the duration of treatment. Elevations in aminotransferases require close attention.**" (emphasis in original)

Reducing the risk of birth defects is another important part of the Letairis risk management program. The Boxed Warning section states that Letairis is **contraindicated in pregnancy.** The risk of serious birth defects is echoed in the CONTRAINDICATIONS, **Pregnancy Category X** section of the PI, which states, "Letairis may cause fetal harm when administered to a pregnant woman" and "Letairis is contraindicated in women who **are or may become** pregnant" (emphasis added). Thus, the statements made by your representative that the risk management plan in place for Letairis "is only there because of the class" and that the risk management plan is "not that big of a deal" severely minimizes the important safety information for Letairis. By minimizing the purpose of the risk management plan and the risks associated with the plan, Gilead misleadingly suggests that Letairis is safer than has been demonstrated by substantial evidence or substantial clinical experience. This implication is particularly concerning given the serious risks associated with the drug.

Conclusion and Requested Action

The oral statements made by your representative are false or misleading and minimize the serious risks associated with Letairis, and thus misbrand Letairis in violation of the Act, 21 U.S.C. 352(f)(1) and (n).

DDMAC requests that Gilead immediately cease promotional activities for Letairis that are the same or similar to those described above. Please submit a written response to this letter on or before March 9, 2009, stating whether you intend to comply with this request, listing all

promotional activities for Letairis that are the same or similar as those described herein and listing all promotional materials (with the 2253 submission date) in use for Letairis as of the date of this letter, identifying which of these materials contain violations such as those described above and explaining your plan for discontinuing such promotional activities. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705, facsimile at (301) 847-8444. In all future correspondence regarding this matter, please refer to MACMIS ID #17248 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Letairis comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Lisa Hubbard, R.Ph.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lisa Hubbard

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